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CT-based intravenous thrombolysis 3-4.5 hours after acute ischemic stroke in clinical practice

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Abstract: **BACKGROUND:** Outcome of stroke patients selected with cerebral computed tomography for intravenous thrombolysis administered in clinical routine from 3 to 4.5 hours after symptoms onset is not well investigated. Aim of this single-center, prospective, observational study was to compare the safety and efficacy of intravenous alteplase given in routine clinical praxis 181-270 minutes (late) and within 180 minutes (early) after stroke onset in patients selected with cerebral computed tomography. **METHODS:** A total of 454 consecutive patients underwent intravenous thrombolysis within 4.5 hours after stroke onset. Sixty of 454 patients were excluded (inclusion in a controlled-randomized trial, n = 51; stroke mimics, n = 9). Of remaining 394 patients, 100 were included in the late group, and 294 were included in the early group. The outcome parameters of symptomatic intracranial hemorrhage at 24 hours, and mortality and favorable outcome (modified Rankin scale score 0-1) at 3 months, and its predictors were investigated. **RESULTS:** In the late cohort, median baseline National Institutes of Health Stroke Scale score was lower (9.5, interquartile range (IQR): 5-13; 11.3, IQR: 6-16; P = 0.01), and median time-to-treatment was longer (209, IQR: 190-222 minutes; 142, IQR: 125-170 minutes; P<0.0001) than in the early group. The incidence of symptomatic intracranial hemorrhage (2.0% versus 2.4%; P = 1.0), death (9.0% versus 9.9%; P = 1.0) and favorable outcome (58.0% versus 51.5%; P = 0.3) did not differ between the late and early cohorts. **CONCLUSION:** These data suggest that intravenous alteplase administered 181-270 minutes after symptoms onset in stroke patients selected with cerebral computed tomography is also beneficial in real-life clinical practice.

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CT-Based Intravenous Thrombolysis 3 to 4.5 Hours After Acute Ischemic Stroke in Clinical Practice

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1 **Background.** Outcome of stroke patients selected with cerebral computed tomography for
2 intravenous thrombolysis administered in clinical routine from 3 to 4.5 hours after symptoms
3 onset is not well investigated. Aim of this single-center, prospective, observational study was to
4 compare the safety and efficacy of intravenous alteplase given in routine clinical praxis 181-270
5 minutes (late) and within 180 minutes (early) after stroke onset in patients selected with
6 cerebral computed tomography.

7
8 **Methods.** A total of 454 consecutive patients underwent intravenous thrombolysis within 4.5
9 hours after stroke onset. Sixty of 454 patients were excluded (inclusion in a controlled-
10 randomized trial, n=51; stroke mimics, n=9). Of remaining 394 patients, 100 were included late,
11 and 294 early. The outcome parameters symptomatic intracranial hemorrhage at 24 hours, and
12 mortality and favorable outcome (modified Rankin scale score 0-1) at 3 months, and its
13 predictors were investigated.

14
15 **Results.** In the late cohort, median baseline National Institutes of Health Stroke Scale score
16 was lower (9.5, interquartile range (IQR) 5-13; 11.3, IQR 6-16; p=0.01), and median time-to-
17 treatment was longer (209, IQR 190-222 minutes; 142, IQR 125-170 minutes; p<0.0001) than
18 in the early group. The incidence of symptomatic intracranial hemorrhage (2.0 vs. 2.4%; p=1.0),
19 death (9.0 vs. 9.9%; p=1.0) and favorable outcome (58.0 vs. 51.5%; p=0.3) did not differ
20 between the late and early cohorts.

21
22 **Conclusion.** These data suggest that intravenous alteplase administered 181 to 270 minutes
23 after symptoms onset in stroke patients selected with cerebral computed tomography is
24 also beneficial in real-life clinical practice.

1 **Introduction**

2 Intravenous (IV) alteplase administered within 3 hours after stroke onset has been shown to be
3 beneficial in a controlled randomized trial (CRT) and a meta-analysis.^{1,2} However, alteplase is
4 still underused which mainly results from the narrow 3-hour therapeutic time window.³ A pooled
5 analysis of six CRTs, which analyzed the outcome of 2775 stroke patients who underwent IVT
6 within 6 hours after symptom onset, was presented at the 27th International Stroke Conference
7 in February 2002 (San Antonio, Texas).² The results suggested that IV alteplase might also be
8 beneficial when administered from 3 to 4.5 hours after stroke onset.² Nonetheless, clinical
9 outcome of stroke patients treated within the aforementioned time window in routine clinical
10 practice was unknown. Furthermore, many centres used magnetic resonance imaging (MRI)
11 mismatch to select stroke patients for IVT administered later than 3 hours after stroke onset.
12 However, CCT was and still is the most common imaging modality used to assess patients
13 presumed to undergo thrombolytic treatment, because it is widely available, fast, easy, and less
14 expensive than MRI. Therefore, we started in March 2002 a prospective, observational study
15 intended to investigate whether IV alteplase is also safe and effective in real-life clinical routine
16 for stroke patients who are selected by CCT and treated between 181 and 270 minutes after
17 symptom onset (late group). It was planned to compare safety and efficacy outcomes of late
18 group patients with those undergoing IVT within 180 minutes after stroke onset (early group).
19 The hypothesis was that the aforementioned outcomes would be similar in the late and early
20 groups.

1 Patients and Methods

2 The Zürich Ischemic Stroke Registry was established in August 1997 to prospectively collect
3 data from all patients admitted with a first ischemic stroke to the Department of Neurology of
4 the University Hospital of Zurich. For this study, we analyzed data of consecutive patients
5 treated with IVT within 4.5 hours after stroke onset between March 2002 and October 2008.

6 All patients underwent the usual evaluation, which included the assessment of medical
7 history, medical and neurological examination including the assessment of stroke severity by
8 the National Institute of Health Stroke Scale (NIHSS) score, routine blood sampling, 12-lead
9 ECG, color duplex sonography of the cerebral arteries and conventional native and contrast-
10 enhanced CCT. Transthoracic and/or transoesophageal echocardiography and 24-hour ECG
11 was performed at the discretion of the treating physician. Stroke etiology was defined was
12 defined according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST)
13 classification system.

14 The following stroke risk factors were differentiated: current cigarette smoking that included
15 by definition cigarette smoking within the last 5 years, former cigarette smoking defined as
16 abstinence from cigarette smoking that started more than 5 years ago, arterial hypertension
17 defined as a history of hypertension (systolic blood pressure >160 mm Hg and/or diastolic
18 blood pressure >90 mm Hg) until September 2000, and systolic blood pressure >140 mm Hg
19 and/or diastolic blood pressure >85 mm Hg since October 2000 measured on 2 separate
20 occasions, or antihypertensive treatment, or both; diabetes mellitus defined as a history of
21 diabetes mellitus, fasting venous plasma glucose concentration of ≤ 7.0 mmol/l on at least 2
22 separate occasions, or venous plasma glucose concentration following the ingestion of 75 g of
23 glucose of ≤ 11.1 mmol/l at 2 h and at one other occasion during the 2-hour test; and
24 hypercholesterolemia, defined as total venous plasma cholesterol level >5.0 mmol/l.

25 Patients were eligible to undergo IVT if they fulfilled the following criteria: age of at least 18
26 years; clinical diagnosis of acute ischemic stroke; time from symptom to treatment onset either
27 0-3 hours or >3 to 4.5 hours; neurological deficit of at least 1 point on the NIHSS. We used the
28 exclusion criteria of the European Cooperative Acute Stroke Study (ECASS) II and III trials with
29 the following exceptions:^{4, 5} age >80 years, seizure during the previous 6 months, oral

anticoagulant therapy with an international normalized ratio ≤ 1.7 , minor stroke symptoms, rapid improvement of symptoms, stupor in basilar artery thrombosis, severe stroke with hemiplegia plus fixed eye deviation, and brain swelling that exceeded one third of the middle cerebral artery (MCA) territory on CCT.

IVT was performed with alteplase 0.9 mg/kg to a maximum of 90 mg with ten percent of the total dose given as a bolus in 1 minute and the remaining 90% delivered in the next hour. All patients were monitored in our stroke unit, where they remained for at least 24 hours. Baseline and demographic characteristics, NIHSS score assessed on admission, latency from symptom onset to IVT, vascular risk factors, medication history and follow-up imaging scans data were prospectively and systematically registered. The clinical outcome after 3 months was assessed by using the modified Rankin scale (mRS).

In March 2002, we extended the time window for IVT with alteplase from 3 to 4.5 hours. If an interventional neuroradiologist was available, patients with suspicion of a symptomatic occlusion of the sphenoidal (M1) or insular (M2) MCA or BA at CCT underwent catheter angiography and in the presence of confirmed occlusion intra-arterial thrombolysis (IAT). The study was performed according to the guidelines of the local ethics committee.

Assessment and definition of symptomatic intracranial hemorrhage

Cerebral CT was routinely done 24 hours after IVT. An emergency CCT was performed in the presence of neurological deterioration. Symptomatic intracranial hemorrhage (sICH) due to IVT was defined as neurological deterioration causing a ≥ 4 points worsening on the NIHSS causally related to ICH detected by CCT within 36 hours after initiation of IVT.

Outcome measurements

Outcome measures were sICH due to IVT, death and favorable outcome (mRS score of 0 or 1 points) 3 months after IVT. The following possible predictors of sICH, death and favorable outcome were examined: age, NIHSS, blood pressure, blood glucose and blood cholesterol levels on admission (continuous variables), and gender, smoking, arterial hypertension,

diabetes mellitus, atrial fibrillation, coronary and peripheral artery disease, and antithrombotic and statin pretreatment (categorical variables).

Statistical analysis

Descriptive statistics for baseline and demographic data were examined. For the comparison of the late vs. the early group, the Fisher-test for dichotomous variables and the Mann-Whitney test for continuous variables was used. Predictors for respective outcome parameters as described above were obtained with uni- and multivariate analyses using multiple logistic regression approaches. We anticipated that there would be much less patients with sICH and deaths than patients with favorable outcome. We thus choose a threshold of $p < 0.05$ for patients with sICH and deaths, and a threshold of $p < 0.1$ for patients with a favorable outcome to select variables from the univariate analysis for the logistic regression model. Significance was declared at $p < 0.05$ level. All tests were performed by using the statistical software package R, version 7.2.7, for Mac OS X.

Results

Between March 2002 and October 2008, 468 consecutive stroke patients underwent thrombolysis, IVT in 454 and IAT in 14 cases. Sixty (13%) of the 454 patients treated with IVT were excluded, because 51 patients were included in an ongoing CRT investigating ultrasound enhanced thrombolysis in MCA occlusion, and 9 patients did not suffer ischemic stroke (so-called "stroke mimic"). Of the 60 excluded patients, four were in the late group (all were stroke mimics), and remaining 56 patients in the early group (51 were included in the aforementioned CRT, and 5 were stroke mimics). Thus, 394 of 454 patients treated with IVT were included, 100 (25%) in the late and 294 (75%) in the early group.

Baseline characteristics of both groups are shown in table 1. In the late group, median baseline NIHSS score was 1.8 points lower (9.5, interquartile range (IQR) 5-13; 11.3, IQR 6-16; $p=0.01$), and median time-to-treatment was 67 minutes longer (median 209, IQR 190-222 minutes; median 142, IQR 125-170 minutes; $p<0.0001$) than in the early group. The other baseline variables did not differ between the two groups. Of the 100 late group patients, 12 (12%) were >80 years of age, and 4 (4%) had warfarin and an $\text{INR} \leq 1.7$ (Table 2).

All but one patient in the early treatment group had 3 months follow-up. Incidence of sICH, death and favorable outcome did not differ between the late and early groups.

Two (2.0%) patients in the early and 7 (2.4%) in the late treatment group experienced a sICH. The difference was statistically not significant ($p=1.0$). Predictors of sICH in univariate analysis were baseline NIHSS score ($p=0.008$) and antithrombotic pre-treatment ($p=0.019$). Both variables remained significant after multivariate analysis (baseline NIHSS score, $p=0.013$; antithrombotic pre-treatment, $p=0.03$).

Nine (9.0%) patients in the early and 29 (9.9%) in the late treatment group died within the 3-month follow-up. The difference was statistically not significant ($p=1.0$). Predictors of mortality in univariate analysis were age ($p=0.0006$), baseline NIHSS score ($p<0.0001$), glycemia ($p=0.03$), atrial fibrillation ($p=0.0002$), cardiac source of embolism ($p=0.019$) and sICH ($p=0.0001$). After multivariate analysis, age ($p=0.01$), baseline NIHSS score ($p=0.0001$) and sICH ($p=0.007$) remained significant predictors of mortality.

Favorable outcome at three months was observed in 151 (51.5%) patients in the early treatment group and in 58 (58.0%) patients in the late treatment group. The difference was statistically not significant ($p=0.3$). Predictors of favorable outcome in univariate analysis were age ($p=0.0001$), baseline NIHSS score ($p<0.0000$), hyperglycemia ($p=0.006$), atrial fibrillation ($p=0.0004$) and lacunar stroke ($p=0.02$). The other variables including time-to-treatment ($p=0.9$) did not reach the level of significance. Multivariate analysis identified age ($p=0.004$) and NIHSS ($p<0.0001$) as independent predictors of favorable outcome.

The outcome parameters of 16 late group patients who fulfilled the exclusion criteria of ECASS III (age >80 years, $n=12$, 12%; warfarin pretreatment and $INR \leq 1.7$, $n=4$, 4%) are shown in Table 2. Compared with the whole late group, those who were >80 years of age or had warfarin with an $INR \leq 1.7$ showed similar baseline NIHSS scores. The older patients had non significant trends to have higher rates of sICH ($p=0.69$) and death at 3 months ($p=0.35$), and a lower rate of favorable 3-month outcome ($p=0.19$) compared to the whole late group.

Estimation of patients who underwent IAT but might have been treated with IVT in the late group: In our stroke unit, IVT is started immediately after plane CCT, and the average time interval between CCT studies and IAT is about 2 hours.⁶ We thus assumed that patients who had the start of IAT between 5.0 and 6.5 hours after symptoms onset would have been candidates for late IVT. IAT was done in 7 of 14 patients in the 5 to 6.5 hours window, in 4 patients earlier, and in 2 patients later. Another patient underwent IAT for the treatment of an occluded basilar artery which did not recanalize after IVT administered within 3 hours after stroke onset.

Discussion

The ECASS III trial and a recent meta-analysis have shown that stroke treatment with IV alteplase is safe and effective between 3 and 4.5 hours after the onset of stroke symptoms.^{5,7} Our results suggest that IV alteplase administered in the same time window in CCT selected stroke patients is also beneficial in real-life clinical routine.

The incidence of sICH, death and favorable outcome were similar in the present late and early treatment groups. These findings are in accordance with the results of two prospective observational studies examining the routine clinical use of IV alteplase from 181 to 270 minutes after stroke onset, the Safe Implementation of Treatments in Stroke - International Stroke Thrombolysis Registry (SITS-ISTR),⁸ and a Dutch single-center study.⁹ In contrast, the rate of sICH causing a neurological impairment of ≥ 4 points on the NIHSS within 48 hours after IVT was lower in the present late group than in ECASS III, SITS-ISTR and the aforementioned Dutch study (Table 3). Risk factors for the development of sICH are older age,¹⁰ history of diabetes,¹¹ current smoking,¹² stroke severity assessed by the NIHSS score,^{13,14} presence and extent of ischemic changes on CCT,¹⁵ high baseline serum glucose,¹¹ and admission fibrinolytic profile.¹⁶ Age, the incidence of diabetes mellitus and current smoking, and baseline blood glucose levels were similar in this study compared to ECASS III, SITS-ISTR and the Dutch study (Table 3), and do not explain the lower rate of sICH in this series. Early ischemic changes on CCT and fibrinolytic profile at admission were not assessed in the present study. Thus, the lower sICH rate in the present study might result from the lower stroke severity at admission, which was an independent predictor of sICH. Finally, the relatively low number of included patients might be another reason for the small amount of sICH in our series. Antithrombotic pre-treatment was an independent predictor of sICH in both the present and the Dutch series.¹⁷

Mortality in our 181-270 hours cohort is within the ranges reported in ECASS III,⁵ a meta-analysis,² and SITS-ISTR (Table 3).⁸ In our multivariate analysis based on 394 patients, baseline NIHSS score was an independent predictor of mortality, which is in accordance with the results of the Dutch study.⁹ ECASS III,⁵ two meta-analyses,^{2,17} and SITS-ISTR did not report predictors of mortality.⁸ In addition, age and sICH were independent predictors of mortality in this series, which is in accordance with the literature.¹⁸

1 The incidence of favorable outcome in our patients treated 181-270 minutes after stroke
2 onset was somewhat higher than in ECASS III and the Dutch study,^{5,9} but clearly more elevated
3 than in SITS-ISTR (Table 3).⁸ Independent predictors of favorable outcome were baseline
4 NIHSS score and age in this series, which is in line with literature.¹⁸ Age did not differ between
5 the aforementioned 3 studies and the present investigation (Table 3). Baseline NIHSS scores
6 were highest in the Dutch study and SITS-ISTR,^{8,9} lower in ECASS III,⁵ and the lowest in the
7 present study. Thus, the high number of patients with a favorable outcome in this study
8 compared to ECASS III, SITS-ISTR and the Dutch study probably results from differences in
9 stroke severity at baseline. The interval from stroke onset to start of IVT was the only
10 independent predictor of a favorable outcome in a meta-analysis, which included 1391 patients
11 treated with IV alteplase in 6 CRTs within 360 minutes after stroke onset.² In contrast, the
12 present, the SITS-ISTR and the Dutch investigators found no similar correlation.^{8,9} The lower
13 number of included patients and the absence of patients who underwent IVT between 4.5 and 6
14 hours after stroke onset might explain the lack of correlation between favorable outcome and
15 time from symptom to treatment onset.

16 An important result of our study is that CCT-based selection of stroke patients supposed to
17 undergo IVT 181 to 270 minutes after symptoms onset seems to be safe and efficient also in
18 real-life clinical practice. In SITS-ISTR,⁸ 80% of treatment decisions in the 3 to 4.5 hours cohort
19 were based on MRI or CCT, and on multimodal imaging in the remaining cases. It is thus not
20 clear how many patients were selected by CCT alone and whether selection using multimodal
21 imaging, MRI or CCT influenced the rates of sICH, mortality or favorable outcome. Our results
22 are in accordance with those of the Dutch study as their patients were also selected with CCT
23 alone.⁹ These findings are important for daily clinical routine management of stroke patients
24 who are candidates for IVT in the 3 to 4.5 hours time window. They suggest that (1) CCT alone
25 is sufficient for assessing most patients with acute ischemic stroke, and (2) the evaluation of
26 the ischemic penumbra with MRI or CT, which is not available in most centers on a 24 hour
27 basis, is not mandatory.

28 In contrast to ECASS III and SITS-ISTR,^{5,8} we included also late group patients who were
29 over 80 years of age or on warfarin and had an INR \leq 1.7 (Table 2). Compared with the whole

late group, older patients presented with a neurological deficit of similar severity, and showed non significant trends for higher rates of sICH and death at 3 months, and a lower rate of favorable 3-month outcome. In Western industrialized countries, more than 50% of strokes occur in patients who are at least 75 years of age.¹⁹ This clearly indicates that CRTs such as the "Third International Stroke Trial" examining the safety and efficacy of IVT in the oldest old stroke patients are urgently needed.²⁰

No late group patient who was on warfarin and had an INR ≤ 1.7 showed a sICH or was dead at 3 months, and 2 patients had a favorable 3-months outcome. These findings suggest that these should be included in further CRTs.

In contradiction of SITS-ISTR,⁸ the distribution of age, hypertension and other vascular risk factors did not differ between the two groups of patients. Baseline NIHSS score was lower in the 181-270 minutes group compared to patients treated earlier. It is likely that the difference in NIHSS scores would have been greater if we would have added the 51 patients who participated in an ongoing ultrasound enhanced thrombolysis trial, since all of them presented with an MCA occlusion. This imbalance in baseline NIHSS score is due to the fact that patients with severe stroke tend to come earlier to emergency service.^{5,8}

The extension of time window from 3 to 4.5 hours increased the rate of patients who underwent IVT in this study by 34% (from 294 to 394 patients), and in the Dutch study even by 74% (from 101 to 176 patients).⁹ Differences in patient referral and management are the most likely causes of the difference in time-to-treatment observed between the Dutch and our study.

One limitation of the present investigation is the relative small sample size of patients treated after 3 hours of stroke onset. Another shortcoming is that patient selection for thrombolytic treatment beyond 3 hours (IVT vs. IAT) was based on individual decision of the treating physician. However, only 7 of 14 patients treated with IAT could have alternatively been treated with IVT. Thus, physician selection of thrombolytic treatment was a minor limitation of this study. A further drawback of this series is that a substantial proportion of patients treated within 181-270 minutes after stroke onset underwent IVT in the first third [IQR, 192-220] of the time period, which is similar to the patients reported in SITS-ISTR.⁸ Thus caution is suggested for an interpretation of the time period from 3.5 to 4.5 hours.

1 In conclusion, the present study indicates that IV alteplase administered 181 to 270 minutes
2 after symptoms onset in stroke patients selected with CCT may also be safe and efficient in
3 daily clinical routine.

Table 1 Baseline characteristics of 394 stroke patients treated with intravenous thrombolysis 181-270 or 0-180 minutes after the onset of symptoms

Time from stroke to treatment [min]	181-270	0-180	P-Value
Patients [n]	100	294	.
Male sex [%]	61	66	0.40
Mean age \pm SD (median; IQR) [years]	65.9 \pm 14.6 (69.0; 58.0–77.0)	65.1 \pm 14.4 (67.0; 55.2–75.0)	0.43
Current smoking [%]	27	29	0.9
Past smoking [%]	12	17	0.27
Hypertension [%]	73	66	0.22
Diabetes mellitus [%]	13	17	0.35
Hypercholesterolemia [%]	48	50	0.81
Coronary artery disease [%]	18	17	0.88
Atrial fibrillation [%]	30.0	27	0.6
Peripheral artery disease [%]	5	5	1.0
Pretreatment Antiplatelet agents [%]	38	33	0.39
Statins [%]	14	23	0.07
Median blood pressure (IQR) Systolic [mm Hg]	150 (135–170)	150 (135–170)	0.95
Diastolic [mm Hg]	85 (80–97)	90 (80–100)	0.35
Median blood glucose (IQR) [mmol/L]	6.0 (5.4–7.0)	6.1 (5.4–7.3)	0.93
Mean NIHSS \pm SD (median; IQR)	9.5 \pm 5.8 (8.0; 5.0–13.0)	11.3 \pm 6.1 (10.0; 6.0–16.0)	0.007
Stroke etiology Cardiac embolism [%]	43	40	0.64
Atherothromboembolism [%]	20	26	0.28
Lacune [%]	7	7	1.0
Other determined [%]	5	5	1.0
Undetermined [%]	27	24	0.59
Mean time to treatment \pm SD (median; IQR) [min]	209 \pm 24 (202; 190–222)	142 \pm 32 (150; 125–170)	<0.0001

IQR denotes interquartile range, and NIHSS National Institute of Health Stroke Scale

Table 2 Presenting characteristics, symptomatic intracranial hemorrhage, mortality and favorable outcome of stroke patients >80 years of age or with warfarin pretreatment and an INR ≤1.7 treated with intravenous alteplase from 181 to 270 minutes after symptoms onset

	>80 Years of Age	Anticoagulation and INR ≤1.7
Patients [n]	12	4
Mean age ± SD (range) [years]	84 ± 2	63 ± 8
Mean NIHSS ± SD	10.0 ± 4.3	11.5 ± 8.3
Symptomatic intracranial hemorrhage [†] [n (%)]	2 (17)	0
Mortality [n (%)]	2 (17)	0
Favorable outcome [‡] [n (%)]	3 (25)	2 (50)

NIHSS denotes National Institute of Health Stroke Scale

[†] increases the National Institute of Health Stroke Scale score by ≥4 points [‡] modified Rankin scale score 0-1 points

Table 3 Presenting characteristics, symptomatic intracranial hemorrhage, mortality and favorable outcome of stroke patients treated with intravenous alteplase from 181 to 270 minutes after symptoms onset in ECASS III, SITS-ISTR, a Dutch study, and the present study

	ECASS III ⁵	SITS-ISTR ⁷	Dutch Study ⁸	Present Study
Type of study	Multicenter, prospective, controlled-randomized	Multicenter, prospective, observational	Monocenter, prospective, observational	Monocenter, prospective, observational
Patients [n]	418	664	75	100
Mean age ± SD (median, IQR) [years]	65 ± 12	(65, 55-73)	68 ± 15	66 ± 15 (69, 58-77)
Male sex [%]	63	60	60	61
Mean NIHSS (median, IQR)	11 ± 6 (9)	- (11, 7-16)	- (12, range 2-35)	10 ± 6 (8, 5-13)
Previous use of antiplatelet agents [%]	31	25	29	38
Hypertension [%]	62	55	45	73
Current smoker [%]	31	28	-	27
Former smoker [%]	21	17	-	12
Diabetes mellitus [%]	15	16	11	13
Hyperlipidemia [%]	-	30	27	48
History of stroke [%]	8	11	16	-
Systolic blood pressure, mean ± SD (median, IQR) [mm Hg]	153 ± 19	- (150, 136-167)	157 ± 24	154 ± 24 (150, 135-170)
Diastolic blood pressure, mean ± SD (median, IQR) [mm Hg]	84 ± 14	- (80, 70-94)	86 ± 18	86 ± 13 85 (80-98)
Mean blood glucose ± SD (median, IQR) [mmol/L]	-	- (6.4, 5.7-7.8)	6.8 ± 2.5	6.0 ± 1.8 (6.6, 5.4-7.0)
Median time to treatment onset (IQR) [min]	239	195 (187-210)	220 (190-220)	202 (190-222)
Symptomatic intracranial hemorrhage [†] within 48 hours (95% CI) [%]	5.3	5.3 (3.8-7.5)	5.3 (2.2-12.9)	2.0 (0-7)
Mortality at 3 months (95% CI) [%]	8	13 (10-16)	-	9 (4-17)
Favorable outcome at 3 months [‡] (95% CI) [%]	52	41 (36-45)	48 (37-59)	58 (48-67)

IQR denotes interquartile range, and NIHSS National Institute of Health Stroke Scale

[†] increases the National Institute of Health Stroke Scale score by ≥4 points [‡] modified Rankin scale score 0-1 points

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